CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Trifloxysulfuron-Sodium

Chemical Code # 5885, Tolerance # 52963
SB 950 # NA

24 May 2004

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, possible adverse effect

Toxicology one-liners are attached.

All record numbers through 209093 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study in review.
File name: T040524
Prepared by Green and Moore, 24 May 2004

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**52963-0114 209064, "24-Months Carcinogenicity and Chronic Toxicity Study in Rats", (R. Gerspach, Toxicology, Novartis Crop Protection AG, Stein, Switzerland, Basel Study No. 971014, Novartis No. 828-97, 26 September 2000). 80 Tif: RAIf (SPF) rats per sex per group received CGA 362622 Technical (94.6% trifloxysulfuron-sodium) in the diet at 0 (basal diet), 50, 500, 2000, and 10000 ppm for 24 months. 10 per sex per group were necropsied at month 12. Average intakes of CGA362622 based on analytical results of test diets were 1.89, 20.2, 82.6, and 429 mg/kg/day for males and 2.27, 23.7, 99.3, and 500 mg/kg/day for females at 50, 500, 2000, and 10000 ppm respectively. Reduced bodyweight ($p < 0.01$) was noted for both sexes at 10000 ppm throughout treatment, beginning at week 4. Food consumption was also decreased at the high dose level. Increased ($p < 0.01$) relative brain and kidney weights in both sexes and heart and liver weights in males were recorded at the high dose level at terminal sacrifice, possibly due to lower bodyweight. Relative kidney weights were also increased in females at 2000 ppm. A treatment-related increase in Leydig cell hyperplasia (11/50 vs. 20/50) ($p < 0.0174$, Cochran-Armitage) was recorded in testes of high dose males at terminal sacrifice. No increase at interim sacrifice. Chronic NOEL = 500 ppm (20.2 and 23.7 mg/kg/day for males and females respectively) (based on an increase in kidney tubular atrophy ($p < 0.0005$) in females at 2000 (13/50 vs 31/50) and 10000 ppm (13/50 vs. 33/50) at terminal sacrifice, not present at interim sacrifice). Incidence of this lesion in males ($p < 0.1401$) was 22/50 vs 23/50 at 2000 and 22/50 vs 25/50 at 10000 ppm. The severity grade for all observations was minimal to slight. No adverse effects. No carcinogenicity. Acceptable. (Green and Gee, 4/14/04).

CHRONIC TOXICITY, DOG

**52963-0112 209061, "12-Month Chronic Dietary Toxicity Study in Beagle Dogs", (B. Altmann, Toxicology, Novartis Crop Protection AG, Stein, Switzerland, Basel Report No. 971012, Novartis No. 1219-98, 2 August 2000). 4 Beagle dogs per sex per group received CGA 362622 Technical (94.6% trifloxysulfuron-sodium) in the diet at 0 (basal diet), 50, 200, 500, 1500, and 4000 ppm for 52 weeks (The overall means based on analytical diet values were 1.72, 6.51, 15.0, 51.1, and 123 mg/kg/day for males and 1.62, 6.91, 14.9, 45.3, and 121 mg/kg/day for females, respectively). Erythrocytes, hemoglobin concentration, and hematocrit were reduced (NS) in males and females at 4000 ppm. Albumin and albumin/globulin ratios were lower (NS) for both sexes at 4000 ppm throughout the treatment period. Aspartate aminotransferase activity was increased ($p<0.01$) and calcium levels were lower ($p<0.05$ and $p<0.01$) for 4000 ppm males. Lower calcium levels (NS) were also recorded for 2 high dose females at week 52. Reduced bilirubin levels were recorded for males (NS) and females ($p<0.05$) at 1500 and 4000 ppm (this was considered reflective of enhanced bilirubin clearance resulting from stimulated glucuronidation of bilirubin secondary to liver enzyme induction). Chloride levels at weeks 13 and 26 were increased ($p<0.01$) for females at 4000 ppm (values fell within the historical control range). Bodyweight and bodyweight change were reduced (NS) for males at 1500 and 4000 ppm. Food consumption was comparable to controls. Relative liver weights were increased for males (NS) and females ($p<0.01$ at 4000 ppm, NS at 1500 ppm) at 1500 and 4000 ppm. Chronic NOEL = 500 ppm (15.0 and 14.9 mg/kg/day for males and females respectively) Based on decreased bodyweight and increased liver weight. Neurological exams were unremarkable. No adverse effects. Acceptable. (Green and Gee, 4/13/04).

ONCOGENICITY, MOUSE

**52963-0113 209063, "18-Month Carcinogenicity Study in Mice", (R. Gerspach, Toxicology, Novartis Crop Protection AG, Stein, Switzerland, Basel study No. 971013, Novartis No. 827-97, 28

July 2000). 60 Tif: MAGf (SPF) mice per sex per group received CGA-362622 Technical (94.6% trifloxysulfuron-sodium) in the diet at 0 (basal diet), 50, 200, 1000, and 7000 ppm for 18-months (5.91, 24.5, 121.2, and 854 mg/kg/day for males and 5.76, 24.1, 111.5, and 818 mg/kg/day for females respectively). No treatment-related effect on clinical signs or mortality. Bodyweight was reduced ($p < 0.01$) for females at 7000 ppm relative to controls. Food consumption was also reduced (NS) for these animals. Chronic NOEL = 1000 ppm (121.2 (males) and 111.5 mg/kg/day (females)) based on decreased bodyweight and food consumption. No treatment-related gross or microscopic findings. An increase in the incidence of nodules in the lungs of high dose females was noted at necropsy. However, there was no treatment-related microscopic correlate. No evidence of carcinogenicity. No adverse effects. Acceptable. (Green and Gee, 4/14/04).

REPRODUCTION, RAT

**52963-0111, 0127, 0106 209060, 209077, 209055, "CGA 362622 Technical: Rat Dietary Two-Generation Reproduction Study", (M. Doubovetzky and J. Gillis, Toxicology, Novartis Crop Protection AG, Stein, Switzerland, Basel Study No. 971016, Novartis No. 829-97, 18 January 2000). 30 Tif; RAIf (SPF) rats per sex per group received CGA 362622 Technical (94.6% trifloxysulfuron-sodium) in the diet at 0 (basal diet), 500, 1000, 8000, and 12000 ppm through 2 generations with 1 litter per generation. Treatment began 10 weeks before mating in both generations. Minimum-maximum mean weekly CGA 362622 intake for F0 males was 24-52, 48-108, 400-823, and 608-1244 mg/kg/day and, for F0 females, 32-100, 65-199, 522-1548, and 806-2374 mg/kg/day at 500, 1000, 8000, and 12000 ppm respectively. Intake for F1 males was 25-70, 49-137, 412-1133, and 652-1755 mg/kg/day; and, for F1 females, 32-97, 60, 199, 500, 1557, and 792-2328 mg/kg/day at 500, 1000, 8000, and 12000 ppm respectively. F0 and F1 Adults. Reduced bodyweight and food consumption were recorded for males (premating) and females (throughout treatment) at 12000 ppm and for males at 8000 ppm. Relative liver, kidney, and brain weights were increased for both sexes at 12000 ppm and for males at 8000 ppm. Hepatocellular hypertrophy (grade 1, minimal) was increased at 8000 and 12000 ppm in both sexes for F0s and for F1 males and at 12000 ppm for F1 females. Parental NOEL = 1000 ppm (48 to 137 and 60 to 199 mg/kg/day (minimum-maximum weekly mean for both generations) for males and females respectively) based on reduced bodyweight and food consumption. F1 and F2 Offspring. Pup growth was delayed (lower day 21 bodyweights) at 8000 and 12000 ppm. Relative spleen and thymus weights were reduced and brain weights were increased at 8000 and 12000 ppm. Reproductive NOEL = 12000 ppm (633 to 1755 and 792 to 2374 mg/kg/day (minimum -maximum weekly mean for both generations) for males and females respectively). No reproductive or fertility effects. No adverse effects. Acceptable. (Green and Gee, 4/12/04).

TERATOLOGY, RAT

**52963-0110, 0128 209059, 209078, "CGA 362622 Technical: Rat Oral Teratogenicity", (M. Doubovetzky, Toxicology, Novartis Crop Protection AG, Stein, Switzerland, Basel Study No. 971019, Novartis No. 817-97, 8 April 1999). 24 mated female Tif: RAI f (SPF) (hybrids of RII/1 x RII/2) rats per group received CGA 362622 Technical (95.7% trifloxysulfuron-sodium, Batch P.702016) by oral gavage at 0 (0.5% aqueous sodium CMC), 30, 300, and 1000 mg/kg/day on gestation days 6 through 15. Maternal food consumption and bodyweight gain were reduced at 300 and 1000 mg/kg/day. Net weight change (carcass weight minus day 6) was lower by 21% at 1000 mg/kg (statistically significant) and by 17% at 300 mg/kg (n.s.). Means of total bodyweights for treated groups, however, were not statistically different from controls. Maternal NOEL = 30 mg/kg/day. Reduced fetal weights were recorded at 300 and 1000 mg/kg/day (0: 5.6 g, 300: 5.3 g (n.s.), 1000: 5.3 g*). Also, treatment related skeletal findings (delayed ossification, etc.) resulting from delayed fetal development secondary to maternal toxicity were noted at 300 and 1000 mg/kg/day. Developmental NOEL = 30 mg/kg/day. No teratogenicity. Acceptable. (Green and Gee, 4/9/04).

TERATOLOGY, RABBIT

**52963-0109, 0131 209058, 209083, "CGA-362622 Technical: Rabbit Oral Teratogenicity", (M. Doubovetzky, Toxicology, Novartis Crop Protection AG, Stein, Switzerland, Basel study No. 971018, Novartis No. 812-97, 28 July 1998). 20 artificially-inseminated Russian Chbb:HM female rabbits were exposed to CGA 362622 Technical (95.7% trifloxysulfuron-sodium, Batch P.702016) at 0 (0.5% aqueous sodium CMC), 50, 100, 250, and 500 mg/kg/day on gestation days 7 through 19. 500 mg/kg/day 3 females aborted (on gestation days 22, 23, and 24). Two were found dead on day 17. No clinical signs were observed for these animals. Four others were sacrificed in extremis during days 16 through 20. Anal and/or genital bloody discharges and presence of blood in the cages and pallor were observed prior to death. The remaining 10 animals of the group were sacrificed prematurely (humane reasons). Bodyweight gain and food consumption were reduced for days 7 - 20. 250 mg/kg/day One female was sacrificed moribund on day 18, another was found dead on day 19. Vaginal blood discharge and/or blood in the cage were observed prior to death. Maternal NOEL = 100 mg/kg/day. Developmental NOEL = 250 mg/kg/day (lack of data at 500 mg/kg/day due to maternal toxicity). No teratogenicity. Acceptable. (Green and Gee, 4/9/04).

GENE MUTATION

**52963-0115 209065, "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test", (E.Deparade, Toxicology, Genetic Toxicology, Novartis Crop Protection AG, Basel, Switzerland, Basel Study No. 971022, Novartis No. 805-97, 8 December 1997). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (plate incorporation) to CGA-362622 Technical (Lot P.702017, 94.6%) in the presence and absence of S9 for 48 hours with a confirmatory assay. *S. typhimurium* strains were exposed at untreated, 0.08, 0.25, 0.76, 2.29, and 6.86 µg/plate and *E. coli* strain WP2 uvrA was exposed at untreated, 61.73, 185.19, 555.56, 1666.67, and 5000 µg/plate. A second assay was performed (plate incorporation was used -S9 and preincubation (30 minutes) was used with S9). Positive controls were functional. No increase in revertants. Acceptable. (Green and Gee, 4/9/04).

**52963-0116 209066, "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test", (E. Deparade, Genetic Toxicology, Novartis Crop Protection AG, Basel, Switzerland, Basel Study No. 991047, Novartis No. 1236-99, 1 December 1999). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (plate incorporation (+/- S9) and preincubation (30 minutes) (+S9) methods) to CGA 362622 WG 75 (74.8% purity, Lot P.902008) in the presence and absence of S9 for 48 hours. *S. typhimurium* strains were exposed at 0 (DMSO), 0.8, 1.6, 3.1, 6.3, 12.5, 25, 50, 100, or 200 µg/plate. *E. coli* WP2 uvrA cultures were treated at 0 (DMSO), 312.5, 625, 1250, 2500, and 5000 µg/plate. There multiple trials. With *Salmonella*, the number of revertants decreased at higher concentrations ± S9, indicating toxicity. Positive controls were functional. No increase in the reversion rate. Acceptable. (Green and Gee, 4/8/04).

**52963-0117 209067, "Gene Mutation Test with Chinese Hamster Cells V79", (B. Ogorek, Toxicology, Genetic Toxicology, Novartis Crop Protection AG, Basel, Switzerland, Basel Study No. 971024, Novartis No. 819-97, 14 October 1997). Chinese Hamster V79 cells (2.5 to 5.0 x 10^6) were exposed in duplicate cultures to CGA 362622 Technical (94.6% trifloxysulfuron-sodium) at 0 (bidistilled water), 148.15, 444.44, 500, 1000, 1333.33, 2000, or 4000 µg/ml, for 5 hours with S9 or for 21 hours without, in two trials. 4000 µg/ml was the limit of solubility for CGA 362622. No increase in the mutation frequency. Positive controls were functional. Acceptable. (Green and Gee, 4/15/04).

CHROMOSOME EFFECTS

**52963-0118 209068, “Cytogenetic Test on Chinese Hamster Cells in Vitro”, (B. Ogorek, Genetic Toxicology, Novartis Crop Protection AG, Basel, Switzerland, Basel study No. 971023, Novartis No. 809-97, 27 January 1998). Quadruple cultures of Chinese Hamster Ovary cells (1 x 10^4 cells/ml (21 hour assays) or 4 x 10^3 cells/ml (45 hour assays)) were exposed to CGA 362622 Technical (94.6% trifloxysulfuron-sodium) at 0 (bidistilled water), 31.25, 62.5, 125, 250, 500, 1000, 2000, and 4000 μg/ml in presence of S9 for 3 hours followed by an 18 or 42 hour recovery period and in the absence of S9 for 21 or 45 hours. 200 metaphases (50, positive controls) with 17 to 21 centromeres from two cultures (100 metaphases per replicate culture, 25 per positive control replicate) were scored. Suppression of mitotic activity was evaluated by counting 2000 cells from one slide each of the treatment and solvent control groups. No increase in structural chromosomal aberrations. Positive controls were functional. Acceptable. (Green and Gee, 4/15/04).

**52963-0119 209069, “Micronucleus Test, Mouse (OECD Conform)”, (E. Deparade, Genetic Toxicology, Novartis Crop Protection AG, Basel, Switzerland, Basel Study No. 971020, Novartis No. 804-97, 10 December 1997). 5 Tif: MAGf (SPF) mice per sex per group received a single gavage dose of CGA 362622 Technical (94.6% trifloxysulfuron-sodium) at 0 (0.5% aqueous carboxymethylcellulose), 1250, 2500, and 5000 mg/kg followed by bone marrow sampling 16, 24, or 48 hours later. 2000 polychromatic erythrocytes were scored per animal. No increase in the frequency of micronucleated polychromatic erythrocytes was indicated. All animals showed ataxia at 16 and 24 hours at 5000 mg/kg and 2/5 females at 48 hours also showed ataxia. No signs were seen at 1250 or 2500 mg/kg. Positive controls were functional. Acceptable. (Green and Gee, 4/15/04).

DNA DAMAGE

**52963-0120 209070, “Autoradiographic DNA Repair Test on Rat Hepatocytes *In Vitro* (OECD Conform)”, (B. Ogorek, Toxicology, Genetic Toxicology, Novartis Crop Protection AG, Basel, Switzerland, Basel Study No. 971021, Novartis No. 802-97, 14 May 1998). Hepatocytes from male TIF:RAI/SPF rats (seeded into 4 compartment multiplates (containing coverslips) per concentration at 10^5 cells/ml/4ml compartment) were exposed to CGA 362622 Technical (94.7% purity, Batch # P.702017) at 0 (DMSO), 0.25, 0.98, 3.91, 7.82, 15.63, 31.25, 62.5, 125, or 250 μg/ml for 16 to 18 hours in two assays. 3 slides (50 cells/slide) were scored. No increase in unscheduled DNA synthesis/repair. Positive controls were functional. Acceptable. (Green and Gee, 4/15/04).

NEUROTOXICITY

Rat Acute Neurotoxicity

52963-0123; 209073; “Acute Oral Neurotoxicity Study in Rats”; (W. Classen; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 991091; 5/11/00); Ten Hanlbm:WIST (SPF) rats/sex/group were dosed orally by gavage with 0, 200, 600 or 2000 mg/kg of CGA 362622 Technical (batch no. P.702016, purity: 95.7%). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related effects were exhibited in any of the functional domains or functional measurements of the functional observational battery. The motor activity assessment did not indicate any treatment-related effects. No histopathological evaluation was performed. **No adverse effect indicated. NOEL:** not assigned due to the lack of a histopathological examination. **Study unacceptable,** possibly upgradeable to acceptable with the submission of the neuropathologic evaluation**.** (Moore, 4/14/04)

52963-0124; 209074; “Acute Oral Neurotoxicity Study in Rats”; (W. Classen; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971107; 12/21/99); Ten Hanlbm:WIST (SPF) rats/sex/group were dosed orally by gavage with 0 or 2000 mg/kg of

CGA 362622 Technical (batch no. P.702016, purity: 95.7%). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related effects were exhibited in any of the functional domains or functional measurements of the functional observational battery. The session totals for total distance, number of movements, movement time, vertical activity, number of rearings, and vertical time in the motor activity assessment were significantly lower for both sexes in the 2000 mg/kg group on the 1st day at 1 to 2 hours post-dose ($p<0.05$). The center time for the 2000 mg/kg males was less than that of the control males ($p<0.05$). In the histopathologic evaluation, one male in the 2000 mg/kg group demonstrated swelling of the myelin sheath in all levels of the spinal cord (grade 3 in the cervical and thoracic segments, grade 1 in the lumbar segment). Another exhibited fiber degeneration in the sciatic (grade 2), tibial (grade 2) and plantar (grade 1) nerves. One female in the 2000 mg/kg group exhibited swelling of the myelin sheath in the thoracic segment of the spinal cord (grade 1). **Possible adverse effect:** neuropathic lesions in the spinal cord and peripheral nerves. **NOEL:** (M/F) < 2000 mg/kg (based upon the treatment-related effects upon motor activity and neuropathic lesions noted for the 2000 mg/kg treatment group). **Study acceptable.** (Moore, 4/13/04)

52963-0137; 209091; "Acute Oral Rangefinding Neurotoxicity Study in Rats"; (W. Classen; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971106; 10/7/98); Three TIF:RAI f (SPF) rats/sex/group were dosed orally by gavage with 0, 2000 or 3500 mg/kg of CGA 362622 Technical (batch no. P. 702016; purity: 95.7%). The test material was prepared in a 0.5% (w/v) of carboxymethylcellulose in an aqueous 0.1% (w/v) polysorbate 80 solution. No deaths resulted from the treatment. No treatment-related effects were noted in the abbreviated functional observational battery which was performed at 1, 2, 4, 6 and 8 hours and once per day thereafter up to day 4. There was no treatment related effect on body weight gain or food consumption. No necropsy examination was performed. A **NOEL** was not assigned. **Study supplemental.** (Moore, 2/23/04)

Rat 90-Day Neurotoxicity Study

52963-0121; 209071; "90-Day Subchronic Neurotoxicity Study in Rats"; (W. Classen; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971108; 3/16/99); Ten Tif: RAif (SPF) rats/sex/group received 0, 2000, 8000 or 16000 ppm of CGA 362622 Technical (batch no. P.702016, purity: 95.7%) in the diet for 3 months ((M): 0, 112, 472, 967 mg/kg/day, (F) 0, 134, 553, 1128 mg/kg/day). No deaths resulted from the treatment. The mean body weights were lower for the males in the 8000 ppm group and for both sexes in the 16000 ppm group. Mean food consumption was lower for the animals in the treated groups during the 1st week of treatment, recovering during the following weeks. There was no treatment-related effect upon the various functional domains, functional measurements in the functional observation battery or motor activity assessment. No lesions were evident in the neuropathological examination. **No adverse effect evident. Subchronic NOEL:** (M) 2000 ppm ((M) 112 mg/kg/day), (F) 8000 ppm (553 mg/kg/day) (based upon lower mean body weights for males in the 8000 ppm treatment group and for the females in the 16000 ppm treatment group); **Study acceptable.** (Moore, 4/15/04)

SUBCHRONIC STUDIES

Rat 90-Day Feeding Study

52963-0106; 209055; "3-Month Oral Toxicity Study in Rats (Administration in the Food)"; (R. Gerspach; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971009; 1/20/98); Ten Tif: RAIf (SPF) rats/sex/group received 0, 100, 1000, 4000, 8000 or 16000 ppm of CGA 362622 Technical (batch no. KI-5180/7; purity: 86.1%) for 13 weeks ((M) 0, 6.14, 65.7, 239, 507 and 1052 mg/kg/day, (F) 0, 7.14, 75.6, 278, 549, 1128 mg/kg/day). Ten additional rats/sex/group received 0 or 16000 ppm of the test material for 13 weeks, followed by a 4 week recovery period. No deaths occurred during the study. The mean body weights and body weight

gains were lower for the 16000 ppm males and female over the course of the study in comparison to the those of the controls ($p<0.01$). The differences were not apparent after the 4 week recovery period. Mean food consumption was lower for both sexes in the 4000 ppm group and above after one week of treatment ($p<0.01$). This effect persisted for both sexes in the 16000 ppm group throughout the study ($p<0.01$). In the hematological evaluation, clotting activity was lower for both sexes in the 16000 ppm group ($p<0.01$), recovering to control levels within 4 weeks. The hemoglobin concentrations of the females in the 8000 and 16000 ppm groups were lower than that of the controls after 13 weeks of treatment ($p<0.01$), recovering within 4 weeks. The mean hematocrit, corpuscular hemoglobin, and corpuscular hemoglobin concentration of the females in the 16000 ppm group were lower than those of the controls ($p<0.01$) at the end of the treatment period, recovering within 4 weeks. The mean number of platelets of the 16000 ppm females was increased after 13 weeks of treatment ($p<0.01$), returning to the control level within 4 weeks. In the clinical chemistry evaluation, the mean serum urea levels were increased for both sexes in the 4000, 8000 and 16000 ppm groups after 13 weeks ($p<0.01$) with the high dose group returning to normal levels by 4 weeks post-treatment. Mean albumin and globulin levels were increased for both sexes in the 16000 ppm group after 13 weeks ($p<0.01$), returning to normal levels within 4 weeks post-treatment. Mean serum sodium and calcium concentrations of both sexes in the 16000 ppm group were elevated above those of the control after 13 weeks ($p<0.01$), returning to control levels during the recovery period. For the 16000 ppm males, the mean chloride and inorganic phosphate levels were conversely lower after 13 weeks than those of the controls ($p<0.01$). The serum cholesterol level for the 16000 ppm males was greater than that of the control after 13 weeks of treatment ($p<0.01$), returning to the control level during the recovery period. The serum triglyceride level for this group was lower than that of the control after the treatment ($p<0.01$), returning to a more comparable level after 4 weeks of recovery. In the necropsy examination, the mean relative liver, kidney, adrenal and testis weights of the 16000 ppm males were greater than those of the controls after 13 weeks of treatment ($p<0.01$). Only the mean relative liver weight was still greater than that of the control after the recovery period ($p<0.01$). For the 16000 ppm females, the mean absolute and relative liver and relative kidney weights were greater than those of the control after 13 weeks ($p<0.01$), with a lowering to control levels after 4 weeks of recovery. In the histological examination, the hepatocellular hyperthrophy in the liver was noted for both sexes in the 8000 and 16000 ppm groups and for the 4000 ppm females after 13 weeks of treatment ((M)): 0/10 vs. 8000: 9/10, 16000: 10/10, (F) 0: 0/10 vs. 4000: 5/10, 8000: 4/10, 16000: 10/10). The hypertrophy had disappeared after 4 weeks of recovery. An increased incidence of single cell necrosis in the liver was noted for the 16000 ppm females after 13 weeks of treatment (0: 1/10 vs. 16000: 3/10). However, after 4 weeks of recovery, there was a greater incidence of the lesion in the control animals (0: 3/10 vs. 16000: 1/10). In the testes of the 16000 ppm males, there was an increased severity of tubular atrophy after the 4 week recovery period. This effect was not evident at the conclusion of the treatment period. The toxicological significance of these latter two observations is not readily apparent. **No adverse effect indicated. Subchronic NOEL:** 1000 ppm ((M) 65.7 mg/kg/day, (F) 75.6 mg/kg/day) (based upon increased serum urea levels and increased hepatocellular hypertrophy in the 4000 ppm group); **Study acceptable.** (Moore, 2/27/04)

Dog 90-Day Feeding Study

52963-0107; 209056; “90-Day Subchronic Dietary Toxicity Study in Beagle Dogs”; (B. Altmann; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971011; 5/30/00); Four beagle dogs/sex/group received 0, 50, 500, 5000, 10000, or 20000 ppm of CGA 362622 Technical (batch no. P. 702016, purity: 95.7%) in the diet for 90 days ((M) 0, 1.74, 19.8, 164.2, 326.2, and 426.7 mg/kg/day, (F) 0, 1.81, 19.6, 167.3, 317.5, and 417.0 mg/kg/day). All of the animals in the 20000 ppm treatment group were euthanized by day 59. These animals suffered reduced food consumption and weight loss and exhibited reduced activity prior to being euthanized. The mean body weight gain over the course of the study was reduced for both sexes in the 5000 and 10000 ppm groups (10000: $p<0.05$, 5000: NS). Food consumption was reduced in a dose-related manner for the three higher treatment groups. In the hematology evaluation, the

females in the 5000, 10000 and 20000 ppm treatment groups had a lower number of red blood cells with a concomitant reduction in hemoglobin concentration and hematocrit ($p<0.05$). For both sexes in these three groups, the animal demonstrated a reduction in total white blood cell count (10000 and 20000: $p<0.05$, 5000: NS). The affected cell types were the neutrophils and eosinophils which demonstrated a reduction in their absolute number and percentage of the total cell count evident at the three higher treatment levels for the females. In the clinical chemistry evaluation, the mean total bilirubin levels for both sexes in the serum of the 5000 ppm and above treatment groups were lower than the levels for the control animals ($p<0.05$). The serum albumin concentrations for both sexes in the 5000 ppm and above treatment groups were lower than those levels of the animals in the control group ($p<0.05$ for the 5000 ppm females and for both sexes in the 10000 and 20000 ppm groups). In contrast, the globulin concentrations were increased for both sexes in the three treatment groups with a corresponding reduction in the albumin/globulin ratio. The mean chloride ion concentration in the serum was elevated in both sexes of the 5000 ppm and above treatment groups ($p<0.05$). In the urinalysis, both sexes in the 10000 and 20000 ppm animals demonstrated a reduction in urinary pH ($p<0.05$ for the 10000 ppm females and both sexes in the 20000 ppm group). The urinary protein urobilinogen and bilirubin levels for both sexes in the 20000 ppm treatment group were greater than those values of the control at 8 weeks of treatment. In the necropsy examination, the mean relative liver weight for the both sexes in 5000 and 10000 ppm treatment groups were increased above those weights for the control ($p<0.05$). The mean absolute liver weight for the 10000 ppm males was also increased above that of the control ($p<0.05$). The mean absolute testes weight for the 10000 ppm males was less than that of the control ($p<0.05$). The mean relative testes weights for the 5000 and 10000 ppm males were less than that of the control (NS). In the histopathological examination, the increased incidence of myeloid hypercellurity was noted in the bone marrow of both sexes in 10000 and 20000 ppm groups and for the females in the 5000 ppm group ((M) 0: 0/4 vs. 10000: 1/4, 20000: 2/4, (F) 0: 0/4 vs. 5000: 2/4, 10000: 2/4, 20000: 3/4). The incidence of thymic atrophy was noted for both sexes in the 5000 ppm and above treatment groups and for the 500 ppm females ((M) 0: 0/4 vs. 5000: 2/4, 10000: 4/4, 20000: 4/4), (F) 0: 0/4 vs. 500: 1/4, 5000: 3/4, 10000: 2/4, 20000: 4/4). A greater incidence and degree of severity was noted for extramedullary hematopoiesis in the liver and spleen for the females in the 5000 ppm and above treatment groups as well (liver: 0: 0/4 vs. 5000: 2/4 (grades 3 and 4), 10000: 2/4 (grades 3 and 4), 20000: 3/4 (grade 2), spleen: 0: 1/4 (grade 1) vs. 5000: 3/4 (grade 1, grade 3 and grade 4), 10000: 3/4 (grade 2 and grade 4 (2)), 20000: 3/4 (grade 2 (2) and grade 4) . The bone marrow hypercellularity, thymic atrophy and extramedullary hematopoiesis correlate with the effects upon the red and white blood cell counts. Hyaline tubular change was noted in the kidneys of both sexes in the 10000 and 20000 ppm treatment groups and for the females in the 5000 ppm group ((M) 0: 0/4 vs. 10000: 2/4, 20000: 2/4, (F) 0: 0/4 vs. 5000: 2/4, 10000: 3/4, 20000: 2/4). This lesion correlates with the renal tubular acidosis as evidenced by the high chloride ion concentration in the serum. Additional histological lesions were increased glycogen content in the liver of both sexes in the 5000 and 10000 ppm groups and reduced spermatogenesis in the testes of the males in the 5000 ppm and above treatment groups. **Possible adverse effects:** reduction in the serum white blood cell count, thymic atrophy and reduced spermatogenesis in the testes; **Subchronic NOEL:** 500 ppm ((M) 19.8 mg/kg/day, (F) 19.6 mg/kg/day) (based upon the reduced white blood cell counts and thymic atrophy in the 5000 ppm treatment group). **Study acceptable.** (Moore, 3/29/04)

Mouse 90-Day Feeding Study

52963-0134; 209087; "3-Month Range Finding Toxicity Study in Mice (Administration in the Food)"; (R. Gerspach; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971008; 3/16/98); Ten Tif: MAGf (SPF) mice/sex/group received 0, 100, 500, 1750, 3500 or 7000 ppm of CGA 362622 Technical (batch no. P. 702016, purity: 95.7%) in the diet for 3 months ((M) 0, 14.2, 67.9, 239, 483 and 1023 mg/kg/day, (F) 0, 20.0, 102, 367, 637, and 1507 mg/kg/day). One male in the 100 ppm treatment group died during the 9th week. There were no treatment-related effects upon the mean body weights or body weight gain. The hematology evaluation did not reveal any treatment-related effects. In the clinical chemistry evaluation, the mean total

bilirubin levels were lower in a dose-related manner. However, this effect was of minimal toxicological significance. There was no treatment-related effect upon mean organ weights or a treatment-related increase in the incidence of lesions in the histology examination. **No adverse effect indicated. Subchronic NOEL (M/F):** 7000 ppm ((M) 1023 mg/kg/day, (F) 1507 mg/kg/day) (based upon the absence of treatment-related effects at the highest dose administered). **Supplemental study** (study protocol did not include all of the parameters required by the subchronic oral toxicity study guidelines). (Moore, 4/5/04)

Rat 28-Repeated Dosing Dermal Toxicity Study

52963-0108; 209057; "4-Week Repeated Dose Dermal Toxicity Study in the Rat"; (R. Gerspach; Toxicology/Experimental Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971007; 3/19/98); The skin of five Tif:RAIf rats/sex/group was exposed to 0, 10, 100 or 1000 mg/kg of CGA 362622 Technical (batch no. P. 702016, purity: 95.7%) for 6 hours/day, 5 days per week for 3 weeks, followed by daily treatment during the 4th week. No deaths resulted from the treatment. The females in the 1000 mg/kg group exhibited lower body weight gain over the course of the study (NS). There was no treatment-related effect upon the food consumption for either sex. No localized dermal irritation was noted at the site of application. In the hematology evaluation, the total white blood cell count and associated counts for the various cell types were reduced in a dose-related manner for the males. This apparent effect was due to the unusually high mean cell counts of the control animals. These control values were outside of the historical range. The chloride ion content in the serum of the high dose males was greater than that of the controls ($p<0.05$) with a concomitant decrease in the inorganic phosphate concentration in the high dose group males ($p<0.05$). The absolute and relative thymic weights for the males were reduced in a dose-related manner ($p<0.05$ for the 100 mg/kg group). However, no microscopic lesions were noted in the histopathological evaluation. **No adverse effect indicated. Systemic NOEL:** 100 mg/kg/day (based upon the increased serum chloride ion concentration and the lower body weight gain demonstrated by the males and females, respectively, in the 1000 mg/kg treatment group). **Study unacceptable**, possibly upgradeable to acceptable with an assurance that the skin was adequately exposed to the test material. (Moore, 4/2/04)

Supplemental Studies

52963-0130; 209082; "28-Day Exploratory Toxicity Study in Male Rats (Gavage)"; (M. Bachmann; Short/Long-term Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 961089; 9/2/96); Five male rats/group were dosed by gavage with 0, 100, 300 or 1000 mg/kg of CGA 362622 Technical (batch no. KI-5180/1, purity: 100%) 5 days per week for 4 weeks. The test material was suspended in an aqueous 0.5% carboxymethylcellulose and 0.1% TWEEN 80 solution. After 4 weeks of treatment, hematology and clinical chemistry parameters were evaluated and the tissues of all of the animals were examined microscopically. No deaths resulted from the treatment. No treatment-related clinical signs were noted. There were no treatment-related effects on mean body weight gain. Although some of the hematology parameters for the treated groups were statistically different those of the control, there was no apparent dose-response relationship. Serum urea levels were increased in a dose-related manner for all treatment groups ($p<0.05$ and $p<0.01$). Mean absolute and relative liver weights for the 1000 mg/kg group were increased over those of the controls ($p<0.05$). Mean absolute and relative thymus weights were decreased over those of the controls ($p<0.05$). In the histopathological examination, the incidence of hepatocellular hypertrophy was evident in the 300 and 1000 mg/kg groups (0: 0/5 vs. 300: 4/5 and 1000: 5/5). Follicular hypertrophy of the thyroid gland was noted for 2 of the 1000 mg/kg animals and for one animal in the 100 mg/kg group. **No adverse effect indicated. NOEL** not assigned; **Study supplemental.** (Moore, 2/24/04)

52963-0136; 209089; "28-Day Range Finding Study in Rats (Administration in the Diet)"; (R. Gerspach; Toxicology/Experimental Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 961123; 5/15/97); Five Tif:RAIf (SPF) rats/sex/group received 0, 1000,

4000, 12000 or 20000 ppm of CGA 362622 Technical (batch no. KI-5180/24, purity: 91%) in the diet for 28 days ((M) 0, 83.0, 323, 1127, 1840 mg/kg/day, (F) 0, 88.3, 362, 1140, 1808 mg/kg/day). Mean body weight gain was lower for the 12000 and 20000 ppm males and for the 20000 ppm females over the course of the study. Mean food consumption was reduced for the 12000 and 20000 ppm females ($p<0.05$ or 0.01). In the hematology evaluation, the mean hemoglobin concentrations and platelet count were increased for both sexes in the 20000 ppm group ($p<0.05$ or 0.01). The platelet count was also increased for the 4000 and 12000 ppm males ($p<0.01$). In the clinical chemistry evaluation, the total bilirubin concentration was lower for both sexes in the 12000 and 20000 ppm groups ($p<0.05$ or 0.01). The mean cholesterol concentrations for the 12000 and 20000 ppm males and for the 20000 ppm female were increased over those of the controls ($p<0.05$ or 0.01). The inorganic phosphate level was reduced for the 20000 ppm males ($p<0.01$). The sodium concentrations for the 4000, 12000 and 20000 ppm males were increased over that of the controls ($p<0.05$ or 0.01). The albumin and globulin concentrations of the 20000 ppm males and the globulin concentration of the 12000 ppm males were increased as well ($p<0.05$). In the necropsy examination, the mean relative liver weights were increased for the 4000, 12000 and 20000 ppm males and for the 20000 ppm females. A microscopic examination of the liver revealed the presence of hepatocellular hypertrophy for the 4000, 12000 and 20000 ppm males and females ((M) 0: 0/5 vs. 4000: 3/5, 12000: 5/5, 20000: 5/5, (F) 0: 0/5, 4000: 3/5, 12000: 4/5, 20000: 5/5). Hepatic cytoplasmic vacuolation and necrosis were also evident for the 20000 ppm males (vacuolation, 0: 0/5 vs. 20000: 3/5, necrosis: 0: 0/5 vs. 20000: 2/5). **Possible adverse effect:** hepatic necrosis; **NOEL(M/F):** 1000 ppm ((M) 83.0 mg/kg/day, (F) 88.3 mg/kg/day) (based upon the increased relative liver weight and hepatocellular hypertrophy noted for the 4000 ppm treatment group). **Supplemental study** (non-guideline study). (Moore, 2/25/04)

52963-0132; 209085; "28-Day Range Finding Toxicity Study in Beagle Dogs"; (B. Altmann; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 970034; 10/28/99); Two beagle dogs/sex/group received 15000 or 30000 ppm of CGA 362622 Technical (batch no. P. 702016, purity: 95.7%) in the diet for 28 days. After 12 days of treatment, the animals in the 30000 ppm group were euthanized due to the severity of their clinical signs. These animals vomited, had hunched posture and weakness in the hindlimbs and/or were recumbent after dosing. These signs were present during the 2nd week. The signs diminished over the course of the day after treatment. Two animals in the 15000 ppm group also demonstrated similar but less severe signs at the same time. The mean body weights gains of the 15000 ppm females and 30000 ppm males and females were lower over the course of their respective treatment periods. The mean food consumption for the 30000 ppm animals was reduced as a consequence of the treatment. In the neurological examination, after 2 weeks of treatment, the 30000 ppm males demonstrated slightly decreased motility, muscle coordination and tone and increased stance width, landing response (front and back), extensor strength, righting from lateral recumbent position and placing reaction (tactile and visual). No effects were noted for the males in the 15000 ppm group after either 2 or 4 weeks of treatment. For the females, the 15000 ppm animals demonstrated decreased motility and muscle coordination after 2 weeks of treatment. They also exhibited a slightly increased stance width, landing response (front and back) and extensor strength. These effects were not evident at 4 weeks. The 30000 ppm females only demonstrated a slightly increased placing reaction at 2 weeks. In the hematological evaluation, the 30000 ppm males exhibited a decrease in the rbc count, hemoglobin concentration and hematocrit after 2 weeks of treatment. The platelet count decreased for both the 15000 ppm and 30000 ppm males after 2 weeks of treatment. After 4 weeks, the count for the 15000 ppm group returned to a near normal level. The rbc count, hemoglobin concentration, and hematocrit were reduced for the 15000 ppm females over the course of the study. These parameters were less affected for the 30000 ppm females. In the necropsy and histopathological examinations, no assessment for the presence of treatment-related lesions was possible due to 1) the lack of a control group and 2) the limited number of study animals/group. **No specific adverse effect was evident. NOEL** not determined. **Study supplemental** (non-guideline study). (Moore, 3/1/04)

52963-0135; 209088; "28-Day Range Finding Toxicity Study in Beagle Dogs"; (B. Altmann;

Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study ID. 971010; 10/29/99); Two beagle dogs/sex/group were dosed orally with 0, 50, 200 or 500 mg/kg/day of CGA 362622 Technical (batch no. P. 702016, purity: 95.7%) in gelatin capsules for 28 days. No deaths resulted from the treatment. There were no treatment related effects upon mean body weight, body weight gain or food consumption over the course of the study. In the hematology evaluation, the mean platelet counts for the 500 mg/kg animals (both sexes) were lower than those of the control animals (NS). In the clinical chemistry evaluation, the albumin concentrations for the 500 mg/kg animals were lower than those of the controls (males, NS; females, $p<0.05$ in trend test). The globulin concentrations for the 500 mg/kg animals were conversely increased over those of the controls (males, NS, females, $p<0.05$ in trend test). The mean total bilirubin in the serum of all of the male treatment groups and for the females in the 200 and 500 mg/kg groups were lower than the levels in the controls. The serum chloride levels for both sexes in the 500 mg/kg group were increased over those of the controls ($p<0.05$ in trend test). The mean calcium level for the males in the 500 mg/kg group was lower than that of the control ($p<0.05$ in trend test). The mean absolute and relative liver weights were greater for the 200 and 500 mg/kg animals in both sexes than those values for the control animals (for absolute weights, $p<0.05$ in trend test for the 500 mg/kg animals and for the 200 mg/kg males). The absolute and relative thymus weights for both sexes in the 500 mg/kg group were lower than those of the controls (for males, $p<0.05$ in trend test). The mean absolute and relative heart weights of the females in the 200 and 500 mg/kg groups were greater than those of the controls (for absolute weights, $p<0.05$ in trend test). In the histopathological evaluation, the incidence of lymphoid follicular hyperplasia in the spleen was noted for the 50 mg/kg females and for both sexes in the higher treatment groups with an increase in severity with greater doses. Reduced spermatogenesis was noted in the testes of one male in the 500 mg/kg group. Cortical atrophy of the thymus for one animal of both sexes in the high dose group. **No adverse effect evident. NOEL** not assigned due to the limited number of animals/group in the study. **Study supplemental** (non-guideline study). (Moore, 4/7/04)

52963-0129; 209079; "CGA 362622: Immunohistochemical Assessment of Hepatic Cytochrome P 450 Isoenzyme in the Course of a 28-day Exploratory Toxicity Study in Rats"; (E. Weber; Toxicology/Cell Biology, Novartis Crop Protection AG, CH-4002 Basle, Switzerland; Study ID. CB 96/27; 12/18/96); Liver samples of 3 male rats each from the control and the 1000 mg/kg group treated with CGA 362622 Technical in a 28-day exploratory toxicity study (Study ID. 961089, vol. no. 52963-0130, rec. no. 209082) were assayed immunohistochemically for cytochrome P450 isoenzymes. Treatment with the test material resulted in a marked induction of CYP2B isoenzymes and a slight increase in the activity levels of the CYP3A and CYP4A isoenzymes. **Supplemental Study.** (Moore, 4/8/04)

52963-0133; 209086; "CGA 362622: Immunohistochemical Assessment of Hepatic Cytochrome P 450 Isoenzymes in the Course of a 3-Month Oral Toxicity Study in Rats"; (E. Weber; Toxicology/Cell Biology, Novartis Crop Protection AG, CH-4002 Basle, Switzerland; Study ID. CB 97/24; 9/3/97); Liver samples of 4 rats/sex/group which were dosed with 0, 4000, 8000 or 16000 ppm of CGA 362622 Technical in a 3-month oral toxicity study (Study ID. 971009, vol. no. 52963-0106, rec. no. 209055) were assayed immunohistochemically for cytochrome P450 CYP2B isoenzymes. Treatment with the test material resulted in a minimal to marked induction of CYP2B isoenzymes with a centrilobular localization progressing to a panlobular distribution in the staining pattern. **Supplemental Study.** (Moore, 4/8/04)

52963-0138; 209093; "CGA 362622: Immunohistochemical Assessment of Hepatic Cytochrome P 450 Isoenzyme CYP2B in the Course of a 28-day Exploratory Toxicity Study in Rats"; (E. Weber; Toxicology/Cell Biology, Novartis Crop Protection AG, CH-4002 Basle, Switzerland; Study ID. CB96/47; 2/10/97); Liver samples of 5 rats/sex/group from the 0, 1000, 4000, 12000 and 20000 ppm groups treated with CGA 362622 Technical in a 28-day exploratory toxicity study (Study ID. 961123, vol. no. 52963-0136, rec. no. 209089) were assayed immunohistochemically for cytochrome P450 CYP2B isoenzymes. Treatment with the test material resulted in a minimal

to marked induction of CYP2B isoenzymes with a centrilobular localization progressing to a panlobular distribution in the staining pattern. Males demonstrated a greater degree of induction. **Supplemental Study.** (Moore, 4/12/04)

METABOLISM STUDIES

52963-0089; 209038; "Metabolism of Pyridinyl-^{14}C-CGA 362622 and Pyrimidinyl-^{14}C-CGA 362622 in Rats"; (T.J. Fleischmann; Covance Laboratories, Inc., Madison, WI and Metabolism Group, Novartis Crop Protection, Inc., Greensboro, NC; Study ID. ABR-98101; 7/15/99); Five Crl:CD(SD)BR rats/sex/group were dosed by gavage with either 0.5 mg/kg of (1) pyridinyl-^{14}C-CGA 362622 (ref. no. CL-XLII-13, specific activity: 53.1 uCi/mg, radiochemical purity: 97.6%, chemical purity: 96.4%) (Group B1) or 100 mg/kg of pyridinyl-^{14}C-CGA 362622 (ref. no. CL-XLIII-17, specific activity: 1.9 uCi/mg, radiochemical purity: 97.9%, chemical purity: 98.4%) (Group D1) or 0.5 mg/kg of (2) pyrimidinyl-^{14}C-CGA 362622 (ref. no. NEH-XVI-84, specific activity: 41.8 uCi/mg, radiochemical purity: 97.0%, chemical purity: 98.3%) (Groups B2, C2) or 100 mg/kg of pyrimidinyl-^{14}C-CGA 362622 (ref. no. CL-XLIII-16, specific activity: 2.0 uCi/mg, radiochemical purity: 97.1%, chemical purity: 95.5%) (Group D2). Animals in Group C2 received 14 pretreatment doses of 100 mg/kg/day of unlabeled CGA 362622 Technical (ref. no. P.702016, chemical purity: 95.7%) prior to treatment with Pyrimidinyl-^{14}C-CGA 362622, 0.5 mg/kg. The vehicle was aqueous 0.025 M sodium bicarbonate. Eighty six to 96% of the radioactivity in the administered dose was recovered in the urine and feces within 24 hours post-dose. Placement of the ^{14}C or different dosages of the test material did not greatly affect the percentages of radiolabel recovered in either the urine or the feces. The percentage of administered dose recovered in the urine ranged from 50 to 61% for the males and from 70 to 79% for the females. The percentage of the administered dose recovered in the feces ranged from 34 to 45% for the males and from 18 to 28% for the females. In the metabolite analysis, the greater percentage of radiolabel recovered in the urine of the females was reflected by the greater recovery of the unmetabolized parent compound. The percentage of the administered dose which was recovered in the urine as parent compound ranged from 10 to 19% for the males and from 36 to 47% for the females. Significant radiolabeling was not found in the tissues and organs at 7 days post-dose. Three mechanisms of biotransformation were evident in the metabolic profile of the test material; oxidative O-demethylation (metabolite J), hydroxylation of the pyrimidine ring and Smile's rearrangement of the sulfonylurea (metabolites D and A). Additional modifications included cleavage of the pyrimidinyl ring (metabolite Q) and secondary conjugation with glucuronide. **Study supplemental** (pharmacokinetic and biliary excretion studies were not performed in order to better characterize the absorption and excretion processes). (Moore, 4/22/04)

52963-0090; 209039; "Biliary Metabolism of [Pyridine-2-^{14}C] and [Pyrimidine-2-^{14}C] CGA-362622 in the Rat"; (T.J. Fleischmann and S. Hassler; Novartis Crop Protection AG, Animal Metabolism Laboratories, CH-4002 Basel, Switzerland and Human Safety Department, Novartis Crop Protection, Inc., Greensboro, NC; Study IDs 482-98 and 037AM01; 5/23/00); Five or six Tif: RAI f (SPF) rats/sex/group were dosed orally by gavage with 0.5 mg/kg of (1) [pyridine-2-^{14}C] CGA 362622 (ref. no. RE-97.5A, specific activity: 47.3 uCi/mg, radiochemical purity: >99%) of (2) [pyrimidine-2-^{14}C] CGA 362622 (ref. no. RE-95.10A, specific activity: 50.8 uCi/mg, radiochemical purity: >95%). The percentage of the administered dose which was absorbed ranged from at least 83 to 88%. Mean recovery of the radiolabel in the bile ranged from 11% for the [pyridine-2-^{14}C] CGA 362622 treated animals (both males and females) to 14 (females) and 27% (males) for the [pyrimidine-2-^{14}C] CGA 362622 treated animals. The percentage of administered dose which was not absorbed ranged from 5 to 8%. The source of the radioactivity recovered in the cage wash, which ranged from 3 to 7% of the administered dose, was not known conclusively. The metabolic pathway included oxidative 0-demethylation (metabolites J, D and A), hydroxylation of the pyrimidine ring (metabolites K and F) and the intramolecular rearrangement of the sulfonylurea bridge (Smile's rearrangement) (CGA-368732). Gluronidation and/or sulfation were secondary conjugation reactions (metabolites N, X, Y_1 and Z). **Study supplemental** (study protocol was

limited to the performance of a biliary excretion study with metabolite identification and quantification). (Moore, 4/27/04)

Note: although the two rat metabolism studies are deemed to be supplemental, there is sufficient information to characterize the pharmacokinetic and metabolic profile of the active ingredient.